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**CADTH RAPID RESPONSE REPORT:**
**SUMMARY WITH CRITICAL APPRAISAL**

# Laser Interstitial Thermal Therapy for Epilepsy and/or Brain Tumours: A Review of Clinical Effectiveness and Cost-Effectiveness


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**About CADTH:** CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

**Funding:** CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

## Abbreviations

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| LITT | laser interstitial thermal therapy |
| LYG | life year gained |
| MR | magnetic resonance |
| SLA | stereotactic laser ablation |
| SRS | stereotactic radiosurgery |
| TLE | temporal lobe epilepsy |

## Context and Policy Issues

Epilepsy is a chronic neurological condition that is characterized by spontaneous seizures that can result in mild symptoms such as a lapse in concentration or may be serious enough to cause unconsciousness or premature death.[1] Between 2010 and 2012, an estimated 139,200 Canadians suffered from epilepsy.[1]

Epilepsy has a diverse etiology ranging from genetic pre-disposition to tumours,[1] and brings a level of complexity to the diagnosis and treatment of the condition. Incidentally, epileptic seizures are associated with epileptogenic zones in the brain which have been the target of treatment options.[2]

The first line of treatment for epilepsy involves the use of anticonvulsant drug therapy, however, one third of patients are unable to experience complete control of their seizures following the administration of two or more pharmaceuticals.[3] For patients with such drug-resistant epilepsy, the primary treatment approach is open surgery (e.g., craniotomy, temporal lobectomy) which seeks to provide relief from seizures by destroying epileptogenic zones or detaching them from other parts of the brain.[4] Fear of possible treatment-related complications such as post-operative neurocognitive decline has inhibited the wide-spread acceptance of open intracranial surgery and prompted interest in alternative techniques.[5]

Laser interstitial thermal therapy (LITT) or stereotactic laser ablation (SLA) is a minimally invasive technique that offers an alternative approach to open surgery for eliminating epileptogenic zones, deep-seated intracranial tumours, and recurrent metastases.[6] LITT involves using high-intensity laser light to induce thermocoagulative necrosis (i.e., destruction of tissue).[7] The laser light is produced by a probe which is made out of an optical fiber tube or flexible catheter with a light-diffusing tip.[4,7] The probe is stereotactically placed over the volume of tissue that is targeted for ablation through a hole that is drilled into the skull.[8,9] The energy from the laser light is converted to heat within the target volume, inducing a cascade of enzymes that leads to protein denaturation, membrane dissolution, and vessel sclerosis, all precursors of necrosis.[10] Since the emergence of intercranial LITT in the 1980s,[11] technical advancements have been made that include the development of cooling systems to control the heat profile of the tip of the laser probe[4] and the use of thermal magnetic resonance (MR) in MR-guided LITT to localize subcentimeter epileptic zones and minimize the target area for laser ablation in real-time.[12] Health Canada has licensed two systems for laser ablation.[13,14] They are the NeuroBlate System[15] and the Visualase MRI-Guided Thermal Ablation System.[16]

A rapid review of the clinical effectiveness and cost-effectiveness of LITT over any comparator for intracranial lesions and epilepsy published by CADTH in 2015 reported that the quantity and quality of the available evidence on clinical efficacy was limited and that no cost-effectiveness studies were identified.[17] This current review aims to summarize updated evidence regarding the clinical effectiveness, safety, and cost-effectiveness of LITT for the treatment of epilepsy and brain tumours.

## Research Questions

1. What is the clinical effectiveness and safety of Laser Interstitial Thermal Therapy for epilepsy and/or for brain tumours?
2. What is the cost-effectiveness of Laser Interstitial Thermal Therapy for epilepsy and/or for brain tumours?

## Key Findings

This review provides evidence that expands upon information previously published by CADTH. Two recent systematic reviews and two prospective cohort studies were identified that addressed the clinical effectiveness and safety of Laser Interstitial Thermal Therapy (LITT) for epilepsy and/or brain tumours. Additionally, one economic evaluation was found that reported on the cost-effectiveness of LITT relative to open craniotomy with or without gliadel wafer, biopsy alone, or open craniotomy and biopsy.

The systematic reviews though well-conducted, included mainly low-quality retrospective primary studies and the prospective studies did not provide comparative evidence on the use of LITT. There was heterogeneity in the patient populations, the configuration of the intervention, the outcomes of interest, and the respective follow-up periods, thereby precluding substantive synthesis. Four of the five studies were financially-sponsored by the manufacturer of one of the LITT systems and the lists of authors included consultants who were employed by the company. For these and other reasons, considerable caution must be taken in making inferences from the results presented in this report.

In summary, the outcomes of interest were seizure freedom, disease progression and overall survival, quality of life, hospitalization, and adverse events. Evidence of limited quality and quantity suggested that LITT proffers no advantage over stereotactic radiosurgery in inducing seizure freedom in patients with drug-resistant, medically-intractable temporal lobe epilepsy. Relative to patients who were treated with stereotactic radiosurgery and craniotomy, patients treated with LITT appeared to experience fewer adverse events and complications. No comparative evidence on disease progression, overall survival, hospitalization, or quality of life was found. None of the studies reported on the incidence of epileptic episodes, post-operative pain, use of medication, or hospital readmissions.

A Markov model-based economic analysis found that LITT was cost-effective relative to a combination of craniotomy and biopsy in treating high grade gliomas in or near areas of eloquence or deep seated tumours. The analysis remained robust to changes in incidence of local recurrence of glioblastomas, the cost of craniotomies for high grade gliomas, the probability of a subtotal resection, and the probability of using a gliadel wafer as adjunctive therapy following a craniotomy.

## Methods

### Literature Search Methods

This report makes use of a literature search strategy developed for a previous CADTH report.[17] For the current report, a limited literature search was conducted by an information specialist on key resources including Medline via OVID, the Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. The search

strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were laser therapy, epilepsy and brain tumours. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2014 and May 16, 2019.

### Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

**Table 1: Selection Criteria**

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| **Population** | Patients with epilepsy and/or brain tumours (all types of epilepsy) |
| **Intervention** | Laser Interstitial Thermal Therapy |
| **Comparator(s)** | • Standard of care (i.e., for epilepsy: craniotomy and removal of epileptic focus; i.e., for brain tumours: craniotomy for tumours and focused radiosurgery)<br>• No comparator |
| **Outcome(s)** | Q1:<br>• Clinical effectiveness (number of epileptic episodes, 'seizure freedom', reduction in post-operative pain, disease progression, reduction in medication, quality of life; length of stay in hospital, hospital readmissions)<br>• Safety<br><br>Q2: cost-effectiveness (e.g., cost-per QALY, cost-effectiveness analysis, cost-utility analysis etc.) |

### Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, if they were duplicates, or if they were included in CADTH's previous related rapid review.[17] Case series and case reports were excluded.

### Critical Appraisal of Individual Studies

The included systematic reviews were critically appraised by one reviewer using the AMSTAR 2,[18] the prospective cohort studies were critically appraised using the Downs and Black checklist,[19] while the economic study was assessed using the Drummond checklist.[20] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described narratively.

## Summary of Evidence

### Quantity of Research Available

A total of 453 citations were identified in the literature search. Following screening of titles and abstracts, 412 citations were excluded and 41 potentially relevant reports from the electronic search were retrieved for full-text review. Two potentially relevant publications were retrieved from the grey literature search and other sources for full text review. Of these 43 potentially relevant articles, 38 publications were excluded for various reasons, and 5 publications met the inclusion criteria for this report. Appendix 1 presents the PRISMA[21] flowchart of the study selection.

### Summary of Study Characteristics

Study characteristics are summarized below and details are available in Appendix 2.

#### *Study Design*

Two systematic reviews,[22,23] two prospective cohort studies,[24,25] and one cost-effectiveness study[26] were included in this review. The systematic reviews were published in 2019[23] and 2016.[22] The prospective cohort studies were published in 2019[24] and 2018,[25] while the cost-effectiveness study was published in 2016.[26]

Each systematic review[22,23] included a meta-analysis of the incidence of adverse events and one of the reviews additionally conducted a meta-analysis of their primary outcome – the incidence of seizure freedom.[23] One review included a randomized controlled trial and 18 retrospective chart reviews, case series, or case reports that were published between 2008 and 2018.[23] The authors assessed the quality and potential likelihood of bias of individual studies using select elements of the modified Newcastle-Ottawa Quality Assessment Scale.[23] A risk of bias assessment was conducted on the body of evidence for each clinical outcome using the Grading of Recommendations Assessment, Development and Evaluation methodology.[23] The main domains of bias that were considered were inconsistency, indirectness, and imprecision.[23] The other review included 20 case series and case reports, and prospective cohort studies published between 1992 and 2015.[22] The authors assessed the quality and potential likelihood of bias of individual studies using the Cochrane Collaboration's tool for assessing risk of bias.[22] Both prospective cohort studies were multicentred and noncomparative.[24,25]

The cost-effectiveness study assessed the impact of LITT relative to open craniotomy and biopsy in patients for whom maximal safe resection may not have been feasible.[26] The impact of treatment was estimated from overall survival rates. As such, the cost-effectiveness ratio outcome was determined from a societal perspective in incremental costs per life year gained ($/LYG) for a hypothetical cohort of patients. Costs and the overall survival rate were discounted at a 3% annual rate (based on the most commonly used discount rate for medical therapies) and projected over a lifetime horizon. The cost-effectiveness ratio was compared with United States and international willingness-to-pay thresholds.

For the base case, the authors constructed a Markov model centred on primary and secondary treatments, adjunctive treatment, treatments for complications, and palliative care pathways following the National Comprehensive Cancer Network Central Nervous System's (NCCN CNS) clinical practice guidelines, estimates of the extent of initial resection (i.e., gross total resection or subtotal resection), estimates of the frequency of a

second surgery, and direct societal costs. The need for a second surgery was a function of progression-free survival time, the Karnofsky Performance Scale scores, and incidence of local recurrent tumours. Adjunctive care, such as chemotherapy and external beam radiation therapy, was a function of the extent of resection, and palliative care with or without chemotherapy was based on the incidence of diffuse tumours, incidence of major complications, and the Karnofsky Performance Scale scores.

Estimates for the independent clinical variables were derived from the published literature. Estimates of direct societal costs were extracted from the 2015 United States' Medicare databases and included average costs of surgery (including costs for in-patient hospital stay and physician services) and adjunctive care. The costs for inpatient treatment were based on a weighted average of use and costs for relevant procedures extracted from the 2012 Medicare database on incidence of the procedures and the 2015 Medicare reimbursement rates, as well as the costs of physician services.

A sensitivity threshold analysis was conducted to determine the effect that changes in various variables had on the incremental cost-effectiveness ratio, namely, the incidence of local recurrence of glioblastomas, the cost of craniotomy for a high grade glioma, the probability of a subtotal resection, and the probability of using a gliadel wafer as adjunctive therapy following a craniotomy. A Monte Carlo simulation was included.

### *Country of Origin*

One systematic review[23] was published by authors in Australia and the United States and one cohort study[24] included authors based in Canada, Denmark, Sweden, and United States. The remaining systematic review, cohort study and cost-effectiveness study were published by authors based solely in the United States.[22,25,26]

### *Patient Population*

#### *Clinical effectiveness*

One systematic review reported on 404 patients with drug-resistant, medically-intractable temporal lobe epilepsy (TLE),[23] and the other reported on 589 patients with high grade tumors in or near areas of eloquence.[22] In the first review, 239 patients with a mean age of 40.9 ± 14 years were treated with LITT; approximately 47% were female.[23] The remaining 165 patients, with a mean age of 29.5 ± 9.7 years, underwent stereotactic radiosurgery (SRS); approximately 57% were female. In the second review, 67 patients were treated with LITT while 522 had open craniotomy.[22] The mean age of the patients treated with LITT was 54.3 ± 10.81 years while that of the other group of patients was 45.6 ± 14.81 years. Approximately 36% of the patients in the LITT arm were female while approximately 41% of those in the craniotomy arm were female.

One prospective cohort study reported on 100 adults and children (58% were females) with primary intracranial tumors, brain metastases, epilepsy, and other unspecified indications,[24] and the other reported on 20 adults (70% were females) with recurrent tumours following SRS for brain metastases.[25] The ages ranged from 10 to 80 years[24] and from 32 to 74 years,[25] respectively.

#### *Cost-effectiveness*

The cost-effectiveness model was based on the treatment of patients with high grade gliomas in or near areas of eloquence or deep seated tumors which are difficult to safely

access and extract through open surgery.[26] The age range of the cohorts of patients on whom the base case was modelled was not disclosed.

### *Interventions and Comparators*

*Clinical effectiveness*

The intervention of interest in all of the studies was LITT[22,23,25] or SLA,[24] with or without MR-guidance. In the remainder of the report, the use of the terms LITT and SLA are used synonymously.

One systematic review included primary studies in which LITT was conducted using either the Neuroblate or Visualase systems, with or without MR-guidance.[22] In the other, LITT was conducted under MR-guidance only; however the authors did not disclose the LITT system that was used in any of the primary studies.[23] The comparators of interest were craniotomy (or open craniotomy)[22] and SRS.[23] Craniotomy refers to manual (often open) resection of the brain to remove tumours or other unwanted tissue. With SRS, focused radiation beams are applied to produce controlled necrosis and neuromodulatory effects in a defined volume of unwanted tissue in the brain.[23]

In the cohort studies, LITT was conducted with the NeuroBlate system only.[24,25]

*Cost-effectiveness*

The cost-effectiveness study compared LITT (plus adjunctive care) to other treatments: (i) craniotomy with or without gliadel wafer placement, (ii) biopsy, and (iii) a combination of craniotomy and biopsy.[26] Adjunctive care included additional therapies, care for complications, hospice care, and palliative care. A description of gliadel wafer placement was not provided nor was there indication that the analysis was limited to a specific LITT system.

### *Outcomes*

*Clinical effectiveness and safety*

The clinical effectiveness of LITT was assessed through seizure freedom,[23] disease progression and overall survival,[25] quality of life,[25] and hospitalization[24,25] and while safety was assessed through adverse events or procedure-related complications.[22-25] Outcomes were reported over a wide range of follow-up periods. One review included studies that followed patients who were treated with MR-guided LITT for a median of 22.4 months (range, 7 to 70 months) and for a median of 43.1 months (range, 24 to 112 months) for those treated with SRS.[23] The second review reported on complication rates that occurred more than 3 months after treatment.[22] The upper threshold of the follow-up period was not indicated. The authors of the prospective cohort studies measured or observed outcomes one month,[24] three months,[25] and at six and a half months[25] following treatment. The outcomes were reported as follows:

- Seizure freedom

Seizure freedom was classified according to the Engel scale ranging from class 1 which represented “freedom from disabling seizures” to class 4 which represented “no worthwhile improvement”.[23] The incidence of seizure freedom referred to the proportion of patients who did not experience a seizure during the period of observation.[23]

- Disease progression and overall survival

Local progression-free survival rate was reported as the proportion of patients who were alive and whose condition had not worsened during the follow-up period.[25] The overall

survival rate was calculated as the proportion of patients who remained alive past the end of the follow-up period.[25]

- Quality of life

Quality of life was measured with the Functional Assessment of Cancer Therapy-Brain scale which is comprised of social wellbeing and emotional wellbeing scores. A decrease in the scores signaled an improvement in quality of life.[25]

- Hospitalization

Duration of hospitalization was reported as the length of stay in the intensive care unit [24] and the mean or median length of stay in the hospital.[24,25]

- Adverse events or procedure-related complications

Both reviews[22,23] and primary studies[24,25] reported on the incidence of safety outcomes. Adverse events or procedure-related complications were described as any undesirable events that occurred during the observation period.[25]

*Cost-effectiveness*

The cost-effectiveness study[26] reported on the benefit of using LITT (plus adjunctive care) over other treatments. The cost (in dollars) per life year gained ($/LYG) was calculated as the ratio of the difference in costs and the difference in overall survival between LITT and the other treatments.

## Summary of Critical Appraisal

The critical appraisal of the studies is summarized below and details are available in Appendix 3.

*Systematic Reviews*

Common strengths of the systematic reviews were that the population, intervention, comparator, and outcomes of interest were described as part of the objectives, multiple databases were searched, keywords for the literature search and search strategies were provided, and the authors critically assessed the quality of the individual included studies. In one of the reviews,[23] the authors further performed study selection and data extraction in duplicate, included the population, intervention, study types, outcomes, and minimum length of follow-up in the study eligibility criteria, and critically assessed the quality of the body of evidence for each outcome. In addition, the sources of funding of the primary studies were reported in supplemental documentation and the authors declared that they had no conflicts of interest.

The authors of the other review provided a list of excluded studies and justification for the exclusion criterial.[22] However, they did not include a conflict of interest statement despite the review being funded by the manufacturer of NeuroBlate LITT system and being employed as consultants for and/or advisory board members of the manufacturing company.[22]

*Prospective cohort studies*

The common strengths of the cohort studies were that they were prospective and clearly described their objectives, population, intervention, and outcomes.[24,25] Registration of their study on a publicly-accessible database suggests that the authors of one of the studies were transparent in their research and minimized patient selection and reporting biases.[24]

The absence of comparative evidence was the primary limitation of these studies.[24,25] Without active comparators, the incremental clinical effectiveness of LITT could not be determined. The study involving 100 patients undergoing SLA reported a 16% loss-to-follow-up rate without an explanation.[24] The second study involving 20 patients, did not report on estimates of the random variability in the data, and had a high loss-to-follow-up rate of 54% (7 out of 20 patients) at three months; thereby limiting the assessment of external and internal validity of the study.[25]

*Cost-effectiveness study*

The authors of the economic evaluation[26] took steps to mitigate bias, as demonstrated by the following. The intervention and its comparators were adequately described, costs were measured in appropriate physical units and future costs and outcomes were adjusted for differential timing through discounting. The costs were extracted from the United States' Medicare (public health) database, an appropriate source of information for an analysis taken from a societal perspective. Allowance was made for uncertainty in estimates of clinical parameters by conducting sensitivity (i.e., multiple scenario) threshold analyses. The clinical parameters that were included in the sensitivity analysis were the proportion of patients in whom open craniotomies were conducted, the cost of open craniotomies for high grade gliomas, the proportion of patients in whom resection was suboptimal, the incidence of gliadel wafer as an adjunctive therapy to craniotomy, and the incidence of local tumour recurrence. It remains unclear whether all relevant costs were included in the model although the observed list of costs appeared extensive.

## Summary of Findings

The main study findings are summarized below while details and authors' conclusions are provided in Appendix 4.

*What is the clinical effectiveness and safety of Laser Interstitial Thermal Therapy for epilepsy and/or for brain tumours?*

*Seizure freedom*

Authors of one systematic review[23] reported that across 18 retrospective chart reviews, case studies and case reports and one RCT that followed patients for 12 to 36 months, there was no statistically significant difference in the mean incidence of seizure freedom in patients with drug-resistant, medically-intractable TLE treated with MR-guided LITT compared with those treated with SRS.

*Disease progression and overall survival*

One of the prospective cohort studies[25] reported that disease had not progressed in 7 out of 13 patients three months following LITT for recurrent brain metastases. An additional tumour responded to radiation therapy and transtuzumab, resulting in a progression-free survival rate of 62% (in an undisclosed number of patients) beyond the 3-month follow-up period.[25] The overall survival rate was 71% at three months of follow-up among 13 patients and 64.5% at six and a half months of follow-up in an undisclosed number of patients.[25] The number of patients lost to follow-up between the first and the final observation points was not disclosed.

*Quality of life*

Based on the component scores, that is, the social wellbeing and emotional wellbeing scores of the Functional Assessment of Cancer Therapy-Brain scale, the quality of life

improved significantly in patients after they were treated with LITT.[25] The combined score did not indicate that LITT offered significant impact. The results for 22 patients who had radiation necrosis were included along with the results for the 20 patients with recurrent tumours.

*Hospitalization*

Both prospective cohort studies reported on the duration of hospitalization.[24,25] Following MR-guided LITT (specifically, SLA), 100 patients with intracranial tumours were hospitalized for a median of 1.1 days (ranging from 0.25 to 25.5 days),[24] which included a median length of stay in the intensive care unit of 0.9 days (ranging from 0 to 14 days).[24] Twenty patients with recurrent brain tumours were hospitalized for a median of 2.3 days (ranging from 1 to 12 days) following MR-guided LITT.[25]

*Safety*

Authors of the clinical effectiveness studies[22-25] reported on the incidence of adverse events or complications in patients with a range of conditions.

*LITT versus SRS:* Across eight case series and case reports of patients with drug-resistant medically-intractable TLE who were treated with MR-guided LITT, complication rates ranged from 10% (3 out of 30 patients) to 35% (7 out of 20 patients) [23] Gait abnormalities were observed in nine patients treated with LITT, cranial nerve deficits in eight, and cerebral hemorrhage in four. An undisclosed number of patients had headaches and nausea. Across one RCT and seven case series and reports of patients treated with SRS, complication rates ranged from 13% (2 out of 15 patients) to 57% (4 out of 7 patients). Eleven of the patients treated with SRS had cerebral edema, seven exhibited psychotic and cognitive symptoms, while two had nerve deficits. Details on the remaining complications were not provided.

*LITT versus craniotomy:* Three (3.9%) out of 77 patients who were treated with LITT in seven single-cohort studies experienced neurocognitive complications.[22] The seven studies ranged in size from 3 to 35 patients. The authors reported the incidence rate as 5.7%. In comparison 141 (13.9%) out of 1036 patients experienced neurocognitive complications after craniotomy in eleven single-cohort studies. The studies ranged in size from 13 to 259 patients.

Neurocognitive complication rates ranged from 0% (0 out 16 patients) to 13% (1 out of 8 patients) in patients with high grade tumors in or near areas of eloquence who were treated with LITT and ranged from 4% (3 out of 67 patients) to 44% (11 out of 25 patients) in patients who had craniotomies.

*Noncomparative LITT:* According to one prospective cohort study, nine (9%) out of 100 patients with tumours and epilepsy had 11 adverse events following SLA.[24] The events included hypoxia from sedation, wide-complex tachycardia in a patient with a history of arrhythmias, wound dehiscence, subdural hematoma, bacteremia, intraventricular hemorrhage, neurological deficits (in two patients), postoperative seizures (in two patients), and delayed intraparenchymal hemorrhage. In addition, one patient with pre-existing intraventricular hemorrhage and hydrocephalus died following SLA. In the second prospective cohort study, three (15%) out of 20 patients with recurrent brain metastases were diagnosed with upper-extremity weakness, slight left facial droop, full body itchiness, and persistent dyspraxia; intracerebral hemorrhage; and weakness following MR-guided LITT.[25]

*What is the cost-effectiveness of Laser Interstitial Thermal Therapy for epilepsy and/or for brain tumours?*

One economic evaluation reported on the cost-effectiveness of LITT over three other treatment options, namely, (i) craniotomy with or without gliadel wafer, (ii) biopsy alone, and (iii) a combination of craniotomy and biopsy.[26] The incremental cost-effectiveness ratios were (i) $8458/LYG, (ii) $48,552/LYG, and (iii) $29,340/LYG, respectively.[26] At an international willingness-to-pay threshold of $32,572/LYG, this meant LITT was cost-effective in an unspecified international setting in comparison to a combination of craniotomy and biopsy.[26] Through a sensitivity analysis exercise, the authors found that LITT remained cost-effective even with higher incidence of local recurrence of glioblastomas and higher cost of craniotomy for high grade gliomas.[26] LITT became less cost effective as the probability of a subtotal resection increased and as the probability of using a gliadel wafer as adjunctive therapy following a craniotomy increased. Nonetheless, LITT dominated craniotomy with gliadel wafer in all scenarios as it was always less costly and more effective.[26]

The authors went further to evaluate the cost-effectiveness of LITT in the United States. They reported that, assuming a willingness-to-pay threshold of $50,000/LYG, LITT would be considered cost-effective relative to a combination of craniotomy and biopsy as well as to biopsy alone.[26] A willingness-to-pay threshold assessment was not conducted specifically for the Canadian healthcare system.

## Limitations

There are five limitations of note in the published body of evidence on clinical effectiveness and safety of LITT for patients with epilepsy and/or for brain tumours. First, the systematic reviews primarily included evidence from low quality, namely retrospective chart reviews, case series and case studies. The value of conducting meta-analyses of evidence from mostly retrospective studies is debatable. Despite being appropriate and possibly the only feasible option for studying chronic conditions with severe, variable, and transient symptoms, retrospective studies are inherently susceptible to patient selection, measurement, and reporting biases.[22] These types of studies generally lack allocation concealment, blinding, and comprehensive reporting of outcomes.[22]

Second, there was considerable heterogeneity in the patient populations and uncertainty about the components of the intervention across the systematic reviews and prospective single-cohort primary studies. The populations were diverse and included patients with drug-resistant, medically-intractable TLE,[23] high grade tumors in or near areas of eloquence,[22] a mix of primary and metastatic tumours and epilepsy,[24] and recurrent metastatic tumours.[25] Descriptions of the components of LITT were not readily available thereby introducing a level of uncertainty in the results; for example, although it was implied, it was not always clear when LITT was conducted under MR-guidance. Given that MR-guidance increases target precision, it is expected to influence LITT outcomes and should therefore be evaluated separately. Combining data from independent prospective cohort studies and reviews of mostly cases is susceptible to confounding by factors ranging from patient selection biases to performance bias; this is especially pertinent given that LITT is conducted mostly in academic medical centres.[22]

The third limitation is that the studies reported on diverse outcomes measured with a variety of scales over a range of follow-up time periods. Each study reported on a subset of relevant outcomes ranging from incidence of seizure freedom, survival, through to duration

of hospitalization and incidence of complications or adverse events. Without reporting on the complete cadre of outcomes, a comprehensive picture of the impact of LITT on any of the included patient populations could not be constructed. Had any of the studies reported on the complete set of outcomes, synthesis would have still been challenging. The reviews spanned an extensive timeframe incorporating information from primary studies that were published in 1992 through to 2018. While only two systems are used worldwide, there is a learning curve associated with LITT that may have influenced its impact on patient outcomes across almost two decades.[26]

The fourth limitation is linked to authorship, study sponsorship, and potential conflict of interest. One systematic review,[22] both cohort studies,[24,25] and the cost-effectiveness study[26] were financially-sponsored by the manufacturer of the NeuroBlate LITT system. All four of these studies had partially overlapping subsets of authors who were consultants for and/or advisory board members of the manufacturing company.[22,24-26] The authors of one of the reviews[22] did not include a conflict of interest statement. They indicated that clinical trials were sought from both licensed LITT systems however, they did not report on the how many included studies included either system. They reported favourable neurocognitive complication rates for LITT compared with craniotomy.[22]

Lastly, with respect to clinical effectiveness and safety, no comparative evidence on disease progression, overall survival, hospitalization, or quality of life was found; neither was there evidence on incidence of epileptic episodes, post-operative pain, use of medication, or hospital readmissions. These limitations suggest that considerable caution must be taken in making inferences about the clinical effectiveness and safety of LITT, specifically in relation to the Canadian context.

Results from the cost-effectiveness analysis must also be viewed with caution due to limitations that were highlighted by the authors.[26] For example, the rate of gliadel wafer implantation may have been overstated, increasing the estimates of costs and survival rates for craniotomies.[26] In addition, the extent of resection, thus, the estimate for overall survival may have been overstated for craniotomies, suggesting that the cost-effectiveness of LITT may have been understated.[26] Furthermore, an assessment of willingness-to-pay was conducted for the United States and for an international context (of unspecified scope), thereby limiting or completely precluding generalizablity of the evidence to the Canadian context.

## Conclusions and Implications for Decision or Policy Making

Two recent systematic reviews[22,23] and two prospective cohort studies[24,25] were identified that were published following CADTH's previous review of the topic.[17] The evidence, drawn primarily from retrospective chart reviews, case series, and case reports, suggested that magnetic resonance-guided LITT proffers no advantage over stereotactic radiosurgery in reducing seizures in patients with drug-resistant, medically-intractable TLE.[23] Also, relative to patients treated with SRS for medically-intractable TLE[23] and craniotomy for high grade tumours in areas of eloquence,[22] patients treated with LITT appeared to experience fewer adverse events and complications. No comparative evidence on disease progression, overall survival, hospitalization, or quality of life was found. Furthermore, none of the studies reported on the incidence of epileptic episodes, post-operative pain, use of medication, or hospital readmissions.

Using a Markov model, LITT was found to be cost-effective in unspecified international settings, relative to a combination of craniotomy and biopsy in treating high grade gliomas

in or near areas of eloquence or deep seated tumours.[26] The analysis remained robust to changes in incidence of local recurrence of glioblastomas in the United States, the cost of craniotomies for high grade gliomas, the probability of a subtotal resection and the probability of using a gliadel wafer as adjunctive therapy following a craniotomy.

Considerable caution must be taken in interpreting the evidence presented in this report due to the paucity of comparative data and other limitations. While the systematic reviews on clinical effectiveness and safety had some noteworthy strengths, there were serious limitations related to the quality of the included primary studies, potential for patient selection, measurement, and reporting biases.[22,23] Importantly, three out of four of the studies on clinical effectiveness and the economic evaluation that were included in this report were financially-sponsored by the manufacturer of one of the LITT systems and their list of authors included consultants who were employed by the company.[22,24-26] These and other limitations introduce a level of uncertainty in the findings and preclude generalizablity of the evidence to the Canadian context. While contemplating the lack of robust findings in the literature and the various limitations, decision-makers and policy makers may also need to consider the impact of training and experience on LITT outcomes[26] and the apparent lack of manufacturing competition. Further research involving prospective study designs or standardized procedures may help to produce evidence that will be useful in informing relevant public health policies in the future.

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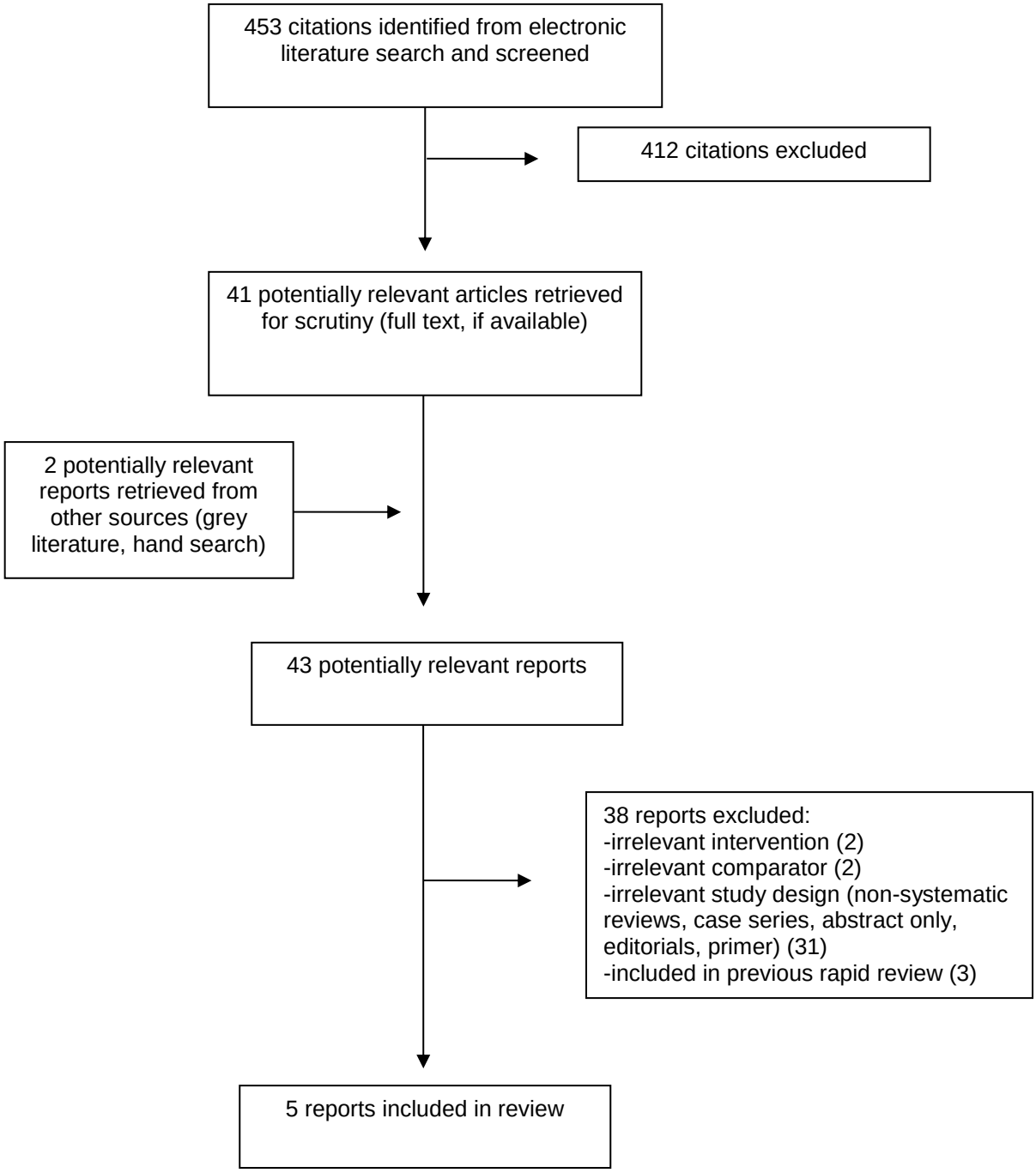
## Appendix 1: Selection of Included Studies



# Appendix 2: Characteristics of Included Publications

## Table 2: Characteristics of the Included Systematic Reviews

| First Author, Publication Year, Country | Study Designs and Numbers of Primary Studies Included | Population Characteristics | Intervention and Comparator(s) | Clinical Outcomes, Length of Follow-Up |
|---|---|---|---|---|
| **Grewal et al., 2019[23]**<br><br>**Australia and United States** | A systematic review and meta-analysis conducted in May 2018; included 9 retrospective case series of patients treated with LITT, and 9 retrospective case series and 1 RCT of patients treated with SRS published between 2008 and 2018 | 404 patients with drug-resistant, medically-intractable TLE | Intervention (n = 239): MR-guided LITT<br><br>Mean age: 40.9 ± 14 years<br><br>% female: 47.1%<br><br>Comparator: (n = 165): SRS<br><br>Mean age: 29.5 ± 9.7 years<br><br>% female: 56.8% | Incidence of seizure freedom and complications[a]<br><br>Follow-up (median): 22.4 months (range, 7 to 70) for MR-guided LITT; 43.1 months (range, 24 to 112) for SRS |
| **Barnett et al., 2016[22,b]**<br><br>**United States** | A systematic review and meta-analysis conducted in April 28, 2015; included 20 prospective and retrospective single cohort studies (8 of patients treated with LITT and 12 of patients treated with craniotomy) published between 1992 and 2015 | 589 patients with high grade tumors in or near areas of eloquence; treated between 1992[c] and 2012 | Intervention (n = 67): LITT (with or without MR-guidance)<br><br>Mean age: 54.3 ± 10.81 years<br><br>% female: 35.8%<br><br>Comparator (n = 522): Craniotomy<br><br>Mean age: 45.6 ± 14.81 years<br><br>% female: 41.2% | Incidence of major neurocognitive complications[d]<br><br>Follow-up: >3 months for major complication rates |

LITT = laser interstitial thermal therapy; MR = magnetic resonance; NR = not reported; RCT = randomized controlled trial; SRS = stereotactic radiosurgery; TLE = temporal lobe epilepsy

[a] Incidence of re-operations was included in the study but not reported in this review
[b] Authors overlap with Ahluwalia et al. (2018)
[c] One study that was published in 1992 did not indicate when its three patients were treated
[d] Includes neurocognitive or functional complications which lasted >3 months following surgery

## Table 3: Characteristics of the Included Primary Clinical Studies

| First Author, Publication Year, Country | Study Design | Population Characteristics | Intervention and Comparator(s) | Clinical Outcomes, Length of Follow-Up |
|---|---|---|---|---|
| **Prospective, Noncomparative Studies** | | | | |
| **Rennert et al., 2019[24,a]**<br><br>**Canada, Denmark, Sweden, and United States** | The Laser Ablation of Abnormal Neurological Tissue using the Robotic NeuroBlate System (LAANTERN) study – a prospective multicentre study | 100 adults and children with primary intracranial tumours (n = 48), brain metastases (n = 34), epilepsy (n = 16), and other unspecified indications (n = 2)<br><br>Mean age: 50.7 ± 17.3 years<br><br>Median age: 52 years (range, 10 to 80)<br><br>% female: 58% | Intervention: MR-guided SLA (Neuroblate)<br><br>Comparator: None | Duration of hospitalization, incidence of adverse events<br><br>Follow-up: 1 month |
| **Ahluwalia et al., 2018[25,b]**<br><br>**United States** | The Laser Ablation After Stereotactic Radiosurgery (LAASAR) study – a prospective, open label, phase II, multicentre study | 20 adults with recurrent tumours following stereotactic radiosurgery for brain metastases[c]<br><br>Mean age: 58.9 ± 11.2 years<br><br>Median age: 60 years (range, 32 to 74)<br><br>% females: 70% | Intervention: MR-guided LITT (Neuroblate)<br><br>Comparator: None | Local PFS, OS, neurocognitive function, quality of life, duration of hospitalization, incidence of adverse events<br><br>Follow-up: 3 months, 6.5 months |

LITT = laser interstitial thermal therapy; MR = magnetic resonance; NR = not reported; OS = overall survival; PFS = progression-free survival; SLA = stereotactic laser ablation

[a] Authors overlap with Ahluwalia et al. (2018)
[b] Authors overlap with Rennert et al. (2019) and Barnett et al. (2016)
[c] Results were reported for 20 adults with recurrent tumours if they were available separately, except for incidence of adverse events

## Table 4: Characteristics of the Included Economic Evaluation

| First Author, Publication Year, Country | Type of Analysis, Time Horizon, Perspective | Decision Problem | Population Characteristics | Intervention and Comparator(s) | Approach | Clinical and Cost Data Used in Analysis | Main Assumptions |
|---|---|---|---|---|---|---|---|
| **Voigt and Barnett, 2016**[26,a]<br><br>**United States** | A CEA over a lifetime time horizon, from a societal perspective | To determine the value (defined as the ICER) of LITT over surgical options | Patients with high grade gliomas in or near areas of eloquence or deep seated tumours where maximal safe resection may not be feasible | LITT vs. current treatments per NCCN CNS guidelines (i.e., craniotomy with or without gliadel wafer, biopsy alone or in combination) | Markov model with sensitivity analysis | OS, complication rates, extent of resection, length of stay were extracted from the published literature<br><br>Direct cost data was extracted from the Medicare database | The willingness-to-pay threshold globally is $2714/month gained or $32,572/LYG |

CEA = cost-effectiveness analysis; CNS = central nervous system; ICER = incremental cost-effectiveness ratio; LITT = laser interstitial thermal therapy; LYG = life year gained; NCCN = National Comprehensive Cancer Network; OS = overall survival

[a] Authors overlap with Barnett et al. (2016)

# Appendix 3: Critical Appraisal of Included Publications

## Table 5: Quality Assessment of the Systematic Reviews using AMSTAR 2[18]

| Strengths | Limitations |
|---|---|
| **Grewal et al., 2019[23]** | |
| • The statement of objectives included the population, intervention, comparator, and outcomes of interest<br>• The authors searched five databases, and provided key words and a search strategy<br>• The authors performed study selection and data extraction in duplicate<br>• The study eligibility criteria included the population, intervention, and minimum length of follow-up<br>• The exclusion criteria included patient characteristics, study types and outcomes of interest<br>• The authors described the populations and parameters of the intervention in detail<br>• The authors critically assessed the quality of individual studies and the body of evidence for each outcome<br>• The sources of funding of the primary studies were reported in supplemental documentation<br>• The authors declared that they had no conflicts of interest | • An explicit statement that the review methods were established prior to the conduct of the review was not provided<br>• The authors did not provide an explanation for their inclusion of specific study designs<br>• The authors did not provide a list of excluded studies nor justification for the exclusion criteria<br>• The authors did not provide descriptions of the study settings |
| **Barnett et al., 2016[22]** | |
| • The statement of objectives included the population, intervention, comparator, and outcomes of interest<br>• The authors searched five databases, and provided key words and a search strategy<br>• The study eligibility criteria included the population, intervention, comparator, and outcomes of interest<br>• The authors provided a detailed description of the reasons studies were excluded<br>• The authors described the populations in detail as provided by the included studies<br>• The authors provided a list of excluded studies and justification for the exclusion criteria<br>• The quality of included studies was assessed with a risk of bias tool | • An explicit statement that the review methods were established prior to the conduct of the review was not provided<br>• The overall level of evidence was not reported for each outcome<br>• A conflict of interest statement was not provided<br>• The authors did not report duplicate study selection<br>• Duplicate data extraction was done sequentially and not independently<br>• The study eligibility criteria did not include study types and outcomes of interest, as such, the authors did not provide an explanation for their inclusion of specific study designs<br>• The authors did not describe the parameters of the intervention<br>• The authors did not provide adequate descriptions of the study settings<br>• A timeframe for follow-up was not clearly specified<br>• The sources of funding of the primary studies were not included |

## Table 6: Quality Assessment of the Primary Studies using the Downs and Black checklist[19]

| Criteria | Rennert et al., 2019[24] | Ahluwalia et al., 2018[25] |
|---|---|---|
| **Reporting** | | |
| 1. Is the hypothesis/aim/objective of the study clearly described? | Yes | Yes |
| 2. Are the main outcomes to be measured clearly described in the Introduction or Methods section? | Yes | Yes |
| 3. Are the characteristics of the patients included in the study clearly described? | Yes | Yes |
| 4. Are the interventions of interest clearly described? | Yes | Yes |
| 5. Are the distributions of principal confounders in each group of subjects to be compared clearly described? | Not applicable | Not applicable |
| 6. Are the main findings of the study clearly described? | Yes | Yes |
| 7. Does the study provide estimates of the random variability in the data for the main outcomes? | Yes | No |
| 8. Have all important adverse events that may be a consequence of the intervention been reported? | Yes | Yes |
| 9. Have the characteristics of patients lost to follow-up been described? | Not applicable | Not applicable |
| 10. Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001? | No | No |
| **External validity** | | |
| 11. Were the subjects asked to participate in the study representative of the entire population from which they were recruited? | Unable to determine | Unable to determine |
| 12. Were those subjects who were prepared to participate representative of the entire population from which they were recruited? | Unable to determine | Unable to determine |
| 13. Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive? | Unable to determine | Unable to determine |
| **Internal validity - bias** | | |
| 14. Was an attempt made to blind study subjects to the intervention they have received? | Not applicable | Not applicable |
| 15. Was an attempt made to blind those measuring the main outcomes of the intervention? | Not applicable | Not applicable |
| 16. If any of the results of the study were based on “data dredging”, was this made clear? | No | No |
| 17. In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls? | Not applicable | Not applicable |

## Table 6: Quality Assessment of the Primary Studies using the Downs and Black checklist[19]

| Criteria | Rennert et al., 2019[24] | Ahluwalia et al., 2018[25] |
|---|---|---|
| 18. Were the statistical tests used to assess the main outcomes appropriate? | Not applicable | Not applicable |
| 19. Was compliance with the intervention(s) reliable? | Unable to determine | Unable to determine |
| 20. Were the main outcome measures used accurate (valid and reliable)? | Yes | Unable to determine |
| **Internal validity – confounding (selection bias)** | | |
| 21. Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population? | Yes | Yes |
| 22. Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time? | Not applicable | Not applicable |
| 23. Were study subjects randomised to intervention groups? | Not applicable | Not applicable |
| 24. Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable? | Not applicable | Not applicable |
| 25. Was there adequate adjustment for confounding in the analyses from which the main findings were drawn? | Not applicable | Not applicable |
| 26. Were losses of patients to follow-up taken into account? | Not applicable | Not applicable |
| **Power** | | |
| 27. Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%? | Not applicable | Not applicable |

## Table 7: Strengths and Limitations of the Economic Evaluation using the Drummond Checklist[20]

| Strengths | Limitations |
|---|---|
| Voigt, 2016[26] | |
| • The study examined the costs and effects of LITT in comparison with suitable alternatives<br>• A societal perspective was indicated<br>• The intervention and its comparators were adequately described. The list of comparatives appeared comprehensive<br>• Costs were measured in appropriate physical units<br>• Future costs and overall survival rates were discounted by 3% - the most commonly used rate for medical therapies<br>• An incremental analysis of the costs and consequences<br>• was conducted<br>• The type of cost analysis used was appropriate<br>• It appears that the costs have been credibly valued considering that the information was extracted from the United States' Medicare (public health) database<br>• Allowance was made for uncertainty in estimates of clinical parameters by conducting sensitivity analyses. The parameters that were varied were: local tumour recurrence, cost of craniotomies, the proportion of patients in whom open craniotomy are conducted and in whom resection is suboptimal, and the incidence of gliadel wafer as an adjunctive therapy following craniotomy | • The costs and effects on survival of complications due to the interventions and comparators were not evaluated. It is unclear whether all relevant costs were included<br>• The rate of gliadel wafer implantation may have been overstated, increasing the estimates of costs and survival rates for craniotomies<br>• The extent of resection rates (thus, the estimate for overall survival) for craniotomy may have been overstated |

LITT = laser interstitial thermal therapy

# Appendix 4: Main Study Findings and Authors' Conclusions

## Table 8: Summary of Findings of the Systematic Reviews

| Main Study Findings | Authors' Conclusion |
|---|---|
| **Grewal et al., 2019[23]** | |
| **Seizure freedom @ 12 to 36 months**<br>**MR-guided LITT (n = 250; 9 retrospective studies) vs. SRS (n = 165; 9 retrospective studies and 1 RCT)**<br>• Mean incidence of seizure freedom: 50% (CI, 44% to 56%; range, 35% to 71%) vs. 42% (CI, 27% to 59%; range, 0% to 73%); *P* = 0.39; indicating that the difference between the groups was not statistically significant[a]<br>• Mean incidence of seizure freedom in patients with lesional epilepsy: 62% (CI, 48% to 74%) vs. 50% (CI, 37% to 64%); *P* = 0.23; indicating that the difference between the groups was not statistically significant[a]<br>• The confidence in the estimates of effects was very low<br><br>**Adverse events**<br>**MR-guided LITT (n = 207; 8 retrospective studies) vs. SRS (n = 150; 7 retrospective studies and 1 RCT)**<br>• Mean incidence of complications: 20% (CI, 14% to 26%) vs. 32% (20% to 46%); *P* = 0.06; indicating no statistically significant difference between the groups with a trend in favour of LITT<br>• Visual field deficits: 12 vs. 21<br>• LITT complications: gait abnormalities (n = 9), cranial nerve deficits (n = 8), cerebral hemorrhage (n = 4), headache and nausea (n = NR)<br>• SRS complications: cerebral edema (n = 11), psychotic and cognitive symptoms (n = 7), and nerve deficits (n = 2)<br>• The confidence in the estimates of effects was very low | "*On the basis of current literature, we found that whereas seizure outcome rates … may be similar between the 2 procedures, [MR-guided] LITT may be associated with lower complication rates. However, more largescale comparative studies are required to validate our findings.*" (p e43) |
| **Barnett et al., 2016[22]** | |
| **Adverse events @ > 3 months**<br>**LITT (n = 77; 8 studies) vs. craniotomy (n = 1036; 12 studies)**<br>• Mean major neurocognitive complication rates (lasting >3 months): 5.7% (CI, 1.8% to 11.6%; $I^2$ = 0%) vs. 13.9% (CI, 10.3% to 17.9%; $I^2$ = 65%)[c,d]<br>• Absolute risk difference: -0.10 (CI, -0.15 to -0.05; *P* < 0.0001); in favour of LITT | *"LITT … may reduce major neurocognitive complications compared to open craniotomy in patients with high-grade gliomas."* (p 172) |

CI = 95% confidence interval; LITT = laser interstitial thermal therapy; LOS = length of (hospital) stay; MR = magnetic resonance; NR = not reported; RCT = randomized controlled trial

[a] These values represent data taken from 18 case series ranging in size from 5 to 58 and one RCT with 31 patients. Caution must be taken in interpreting these results as treatment may have been conducted in a variety of settings. Insufficient information on the homogeneity of the study characteristics was available to assess the estimates of effect adequately.
[b] These values represent data from 15 case series and one RCT with 31 patients
[c] Values reported in text format were different from those presented in tabular format: 3.9% (3/77) vs. 13.6% (141/1036)
[d] The $I^2$ value reflects significant heterogeneity across the craniotomy studies, suggesting caution must be taken in using the estimate of effect

## Table 9: Summary of Findings of the Primary Clinical Studies

| Main Study Findings | Authors' Conclusion |
|---|---|
| **Prospective, noncomparative studies** | |
| **Rennert et al., 2019[24]** | |
| **Duration of hospitalization (n = 84)[a]**<br>Median LOS (days): 1.1 (range, 0.25 to 25.5)<br>Mean LOS (hours): 2.55 ± 3.63<br><br>Median length of intensive care unit stay (days): 0.9 (range, 0.0 to 14)<br>Mean length of intensive care unit stay (days): 1.6 ± 2.6<br><br>**Adverse events**<br>Incidence of adverse events: 11% (n = 9 patients); neurological deficits (n = 2 patients), postoperative seizures (n = 2 patients), hypoxia from sedation, wide-complex tachycardia in a patient with a history of arrhythmias, wound dehiscence, subdural hematoma, bacteremia, intraventricular hemorrhage, delayed intraparenchymal hemorrhage, death from intraventricular hemorrhage with hydrocephalus observed prior to SLA, in one patient each | *"Analysis of the first 100 patients from the […] registry suggests that SLA is a safe, minimally invasive procedure for the treatment of intracranial pathologies. The morbidity and hospitalization time profiles compare favorably to those previously reported for conventional craniotomies."* (p 9) |
| **Ahluwalia et al., 2018[25]** | |
| **Disease progression[b]**<br>Local PFS rate @ 3 months (n=13): 54%<br>Local PFS rate beyond 3 months (n=NR): 62%, reflecting complete response of one tumour following radiation therapy and transtuzumab<br><br>OS rate @ 3 months (n=13): 71%<br>OS rate @ 6.5 months (n=NR): 64.5%<br><br>**Quality of life**<br>A statistically significant decline was observed in social wellbeing and emotional wellbeing scores, suggesting an improvement in quality of life.[c]<br>The composite score did not indicate significant impact.<br><br>**Duration of hospitalization (n=20)**<br>Median LOS: 2.3 days (range 1 to 12 days)<br><br>**Incidence of adverse events (n=20)[d]**<br>Left upper-extremity weakness, slight left facial droop, full body itchiness, and persistent dyspraxia: 1<br>Intracerebral hemorrhage: 1<br>Weakness: 1<br><br>Results that were presented separately for 22 patients with radiation necrosis was not included in this report. Also, data on change in neurocognitive function was not included as data was not reported separately for patients with recurrent tumours. | "*In summary, this prospective study confirmed that LITT is a low-risk surgical procedure that can control radiographic lesion growth after SRS in patients with brain metastases and should be considered in those who are surgically eligible. Further studies with a control group for better characterization of possible benefits are warranted.*" (p 810) |

LITT = laser interstitial thermal therapy; LOS = length of (hospital) stay; OS = overall survival; PFS = progression-free survival; SLA = stereotactic laser ablation; SRS = stereotactic radiosurgery

[a] Data on length of stay was missing from sixteen patients
[b] The reasons seven patients discontinued treatment were not reported
[c] The scores included results from 22 patients with radiation necrosis; results for 20 patients with primary tumours were not separately reported
[d] Post-operative safety outcomes are not included here as they were not separately reported for the tumour group

## Table 10: Summary of Findings of the Included Economic Evaluation

| Main Study Findings | Authors' Conclusion |
|---|---|
| Voigt, 2016[26] | |
| **Incremental cost-effectiveness ratio**<br>The cost-effectiveness of LITT over: (i) craniotomy with or without gliadel wafer only, (ii) biopsy only, and (iii) a combination of craniotomy and biopsy was $8458/LYG, $48,552/LYG, and $29,340/LYG, respectively.<br><br>At an international willingness-to-pay threshold of $32,572/LYG, this means LITT was cost-effective in comparison to a combination of craniotomy and biopsy.<br><br>**Sensitivity analysis**<br>LITT was more cost-effective even with higher incidence of local recurrence of glioblastomas and higher cost of craniotomy for a high grade gliomas.<br><br>LITT became less cost effective as the probability of a subtotal resection increased and as the probability of using a gliadel wafer as adjunctive therapy following a craniotomy increased.<br><br>LITT dominated craniotomy with gliadel wafer as the former was less costly and more effective | "*The use of brain LITT under magnetic resonance imaging guidance in complex craniotomies where high-grade gliomas reside in or near areas of eloquence (or where these types of tumors are deep seated) appears to be cost effective*" (p 16) |

LITT = laser interstitial thermal therapy; LYG = life year gained